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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/686,092	10/14/2003	Karen W. Shannon	10030468-1	6820

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EXAMINER	
WHALEY, PABLO S	
ART UNIT	**PAPER NUMBER**
1631	

MAIL DATE	DELIVERY MODE
08/03/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/686,092	SHANNON, KAREN W.	
	Examiner	Art Unit	
	Pablo Whaley	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2007 and 24 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-16 and 26-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6-16 and 26-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

REQUEST FOR CONTINUED EXAMINATION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/24/2007 has been entered.

CLAIMS UNDER EXAMINATION

Claims herein under examination are claims 1-4, 6-16 and 26-30. Claims 17-25 have been cancelled. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied, as necessitated by amendment. They constitute the complete set presently being applied to the instant application.

CLAIM REJECTIONS - 35 USC § 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 6-16, and 26-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1 and 26 are rejected for the following reasons. Claims that depend directly or indirectly from claims 1 and 26 are also rejected herein due to said dependence. The following rejections are either reiterated or newly applied, as necessitated by amendment.

Claim 1 (step a) recites "identifying...candidate probe sequences." Claim 1 (step b) later recites "providing an array of candidate nucleic acid probes immobilized on a surface." It is unclear if these are intended to be the same candidate sequences from "step a", or different candidate probes. Clarification is requested via clearer claim language.

Claim 1 (step ii) recites "to produce gene expression data." This claim uses passive language (i.e. to produce). Therefore, it is unclear whether applicant intends for this to be an active method step (i.e. producing), an intended use, or a further limitation of the claimed method. Clarification is requested via clearer claim language.

Claim 1 and 26 (step c) recite "to produce clustered probe sequence." This claim uses passive language (i.e. to produce). Therefore, it is unclear whether applicant intends for this to be an active method step (i.e. producing), an intended use, or a further limitation of the claimed method. Clarification is requested via clearer claim language.

Claims 1 and 26 (step d) recite "to identify any candidate probe sequences." This claim uses passive language (i.e. to identify). Therefore, it is unclear whether applicant intends for this

to be an active method step (i.e. identifying), an intended use, or a further limitation of the claimed method. Clarification is requested via clearer claim language.

Claim 1 is directed to methods for "identifying a sequence of a nucleic acid." However, claim 1results in a step of "evaluating any remaining candidate probe sequences not among said clustered probe sequences." Therefore it is unclear in what way the claimed method achieves the purpose of the preamble. Clarification is requested.

CLAIM REJECTIONS - 35 USC § 101

Claims 26-30 were rejected under 35 U.S.C. 101 because these claims are drawn to non-statutory subject matter. Applicant's arguments, filed 03/23/2007, are persuasive in view of the amendment to instant claim 26 (step f). This rejection is hereby withdrawn.

CLAIM REJECTIONS - 35 USC §112, 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-16 and 26-30 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. Applicant's arguments, filed 03/23/2007, are persuasive in view of the amendments to instant claims 1 and 26. This rejection is hereby withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 6-10, 12-16, and 26-30 are rejected under 35 U.S.C. 103(a) as being made obvious by Li et al. (Bioinformatics, 2001, Vol. 17, No. 11, p.1067-1076), in view of Ben-dor et al. (Journal of Computational Biology, 1999, Vol. 6, No. ¾, p. 281-297).

Li et al. teach a computer-implemented method and program called "ProbeSelect" for selecting an optimal number of DNA oligos for gene expression arrays. Identification and selection of candidate probes is based on selection criteria [Abstract, Fig. 2, and Table 1] based on frequency matching [p.1070, Col. 2, ¶ 2], free energy calculation [p.1071, Col. 1, ¶ 3], and sequence matching (and mismatching) [p.1071, Col. 1, ¶ 2], which are teachings for selection

based on base composition and lack of homology, as in claims 1, 2, 26, and 27 (ii and iii). It is noted that selection of mismatch sequences is interpreted as a teaching for 'lack of homology, as in claims 2 and 27 (step iii). Selection criteria directed to frequency calculation [p.1071, Col. 1, ¶1] and free energy calculation [p.1072, Col. 1, ¶1] and [Table 4], are teachings for empirical evaluation as in claims 1 and 26. Candidate probes are evaluated using three different model organisms (i.e. experimental conditions), including *E. coli* bacterial cell lines [p.1074, Col. 1, ¶1], as in claims 1, 6, 12, and 26. The "ProbeSelect" computer program as described equates to a computational analysis system [p.1069, Col. 2, ¶3], as in claims 14, 15, 16, and 30. Optimal probes are output to a user [Table 1 and 2], as in claim 26 (steps e and f). Li et al. also teach subjecting arrays to experimental conditions for producing gene expression data [p.1067, Col. 2, DNA chips].

Li et al. does not specifically teach limitations directed to evaluating gene expression data based on clustering, as in claims 1 and 26 (step c and d), and claims 7, 8, 9, 13, 26, 28, and 29.

Ben-dor et al. teach methods for analyzing gene expression patterns using clustering algorithms [Abstract]. More specifically, steps of analysis include determination of the gene expression data (i.e. expression vector) and representing data by a real-valued expression matrix comprising a measured expression level of gene *i* in experimental (condition) *j*, deriving a similarity matrix, clustering genes based on the similarity data or on the expression data [p.282, ¶3], and displaying results [p.291, Fig. A-C], as in claims 1 (step c), 7, 26 (step c, e, and f), and 28. The cluster algorithm also provides for evaluation of matching data and "negative" matching candidate probe data [p.288, lines 5-10], which is interpreted as a teaching for probes not among said clustered probes, as in claims 1 and 26 (step d), and Jaccard coefficient evaluation wherein unmatched data is not analyzed [p.288, lines 7-10], as in claim 13. Ben-dor et al. also

teach clustering of candidate with substantially the same expression patterns [p.291, Fig. A and B] and use of affinity thresholds [p.291, ¶2], as in claims 8, 9, and 29.

Thus it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the optimal array probe selection method of Li et al. using the clustering method of Ben-dor et al. to rapidly analyze gene expression data produced by candidate probes in order to provide additional information for ensuring selection of optimal probes [Li et al., p.1076, Col. 1, ¶1], resulting in the practice of the instant claimed invention. One of skill in the art would have had a reasonable expectation of successfully combining the above teachings as both Li et al. and Ben-dor et al. clearly teach microarrays, probes, and methods of analyzing gene expression data.

Claims 1-4, 7-9, 13-16, and 26-30 are rejected under 35 U.S.C. 103(a) as being made obvious by Sung et al. (Proceedings of the Computational Systems Bioinformatics (CSB'03), 11-14 August 2003, p.1-10), in view of Ben-dor et al. (Journal of Computational Biology, 1999, Vol. 6, No. ¾, p. 281-297).

Sung et al. teach a computer-implemented method for designing probes for microarrays [Abstract]. Identifying probes using a program (i.e. FindProbe), wherein three selection criteria are used [Section 2.1 and 2.2] based on homogeneity (i.e. base content), proximity to 3' end of probes [Section 4: Sensitivity filtering], and matching and mismatching of sequences (i.e. lack of homology) [Section 5.2], as in claims 1, 2, 3, and 27. It is noted that sensitivity filtering reduced probes that form secondary structures (i.e. overlap) [Section 4], and therefore has been broadly interpreted as a teaching for minimization of candidate probes that overlap with each other, as in claim 4. Empirically evaluating an array of candidate probes are evaluated under and

subjected to different experimental conditions [Table 2 and 5] and [Section 6, ¶2], as in claims 1 and 26 (step b). The "FindProbe" program is a teaching for a computational system, as in claims 14-16 and 30.

Sung et al. does not specifically teach limitations directed to evaluating gene expression data based on clustering, as in claims 1 (steps c and d) and 26, and claims 7, 8, 9, 13, 26, 28, and 29.

Ben-dor et al. teach methods for analyzing gene expression patterns using clustering algorithms [Abstract]. More specifically, steps of analysis include determination of the gene expression data (i.e. expression vector) and representing data by a real-valued expression matrix comprising a measured expression level of gene *i* in experimental (condition) *j*, deriving a similarity matrix, clustering genes based on the similarity data or on the expression data [p.282, ¶3], and displaying results [p.291, Fig. A-C], as in claims 1 (step c), 7, 26 (step c, e, and f), and 28. The cluster algorithm also provides for evaluation of matching data and "negative" matching candidate probe data [p.288, lines 5-10], which is interpreted as a teaching for probes not among said clustered probes, as in claims 1 and 26 (step d), and Jaccard coefficient evaluation wherein unmatched data is not analyzed [p.288, lines 7-10], as in claim 13. Ben-dor et al. also teach clustering of candidate with substantially the same expression patterns [p.291, Fig. A and B] and use of affinity thresholds [p.291, ¶2], as in claims 8, 9, and 29.

Thus it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the probe selection method of Sung et al. using the clustering method of Ben-dor et al. to rapidly analyze gene expression data produced by candidate probes in order to ensure that all candidate probes produce the expected expression patterns [Ben-dor et al., Abstract], resulting in the practice of the instant claimed invention. One of skill in the art would have had a reasonable expectation of successfully combining the above teachings as

both Sung et al. and Ben-dor et al. clearly teach microarray technology and algorithms for analyzing probe data.

Claims 10 and 11 are rejected under 35 U.S.C. 103(a) as being made obvious by Li et al. (Bioinformatics, 2001, Vol. 17, No. 11, p.1067-1076), in view of Ben-dor et al. (Journal of Computational Biology, 1999, Vol. 6, No. ¾, p. 281-297), as applied to claims 1, 2, 6-10, 12-16, and 26-30, above, and further in view of Cao et al. (Cross Comparison of DNA Microarray Platforms, Alliance for Cellular Signaling Laboratories, Sept. 26, 2003, p.1-23).

Li et al. and Ben-dor et al. make obvious a method for selecting an optimal number of probes for use in gene expression arrays, as set forth above and applied to claims 1, 2, 6-10, 12-16, and 26-30.

Li et al. and Ben-dor et al. do not specifically teach log-ratio limitation as in claims 10 and 11. However, Ben-dor et al. clearly teach and suggest the calculation of log-ratios of intensities [p.292, ¶ 1].

Cao et al. teach a method for comparing the reproducibility and sensitivity of several microarray platforms, including the Affymetrix GeneChip, custom cDNA arrays, and custom oligo arrays [Abstract]. More specifically, Cao et al. teach calculation of "log-ratio" values across a number of different experimental conditions [p.8] and values in the range of –0.16 to 0.44 [p.10], as in claims 10 and 11.

Thus it would have been obvious to someone of ordinary skill in the art at the time of the instant invention to practice the probe selection method of Li et al. using the clustering method of Ben-dor et al. and the log-ratio calculations taught by Cao et al. in order to compare gene expression data for optimal probes that are selected using different platforms [Cao et al., p.6],

resulting in the practice of the instant claimed invention. One of skill in the art would have had a reasonable expectation of successfully combining the above teachings as all teach microarray technology and algorithms for analyzing probe data.

Provisional Obviousness-Type Double Patenting Rejection

The non-statutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 C.F.R. 1.321 (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. 3.73(b).

Claims 1-4, 6-16 and 26-30 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-11 of co-pending Application No. 10/871,303. Although the conflicting claims are not identical, they are not patentably distinct from each other because of the broadly encompassing scope of the instantly claimed invention causing the inventions to have overlapping embodiments. The instant claims and those of '303 recite the same method steps, with minor variations. For

example, instant claims 1 and 26 are directed to methods for identifying a sequence of nucleic acid suitable for use as a normalization probe, which require evaluation of clustering and evaluation of data not in clustered data, whereas claims 1-11 of co-pending of '303 are directed to a method for identifying and selecting nucleic acid probes, which require selecting probes, forming of clusters based on hybridization data, and identifying clusters not in a Supercluster. Therefore, It would have been obvious to someone of ordinary skill in the art at the time of the instant invention evaluate Superclusters and data not in superclusters, as evaluating cluster gene expression data and hybridization data are well-known in the art. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

CONCLUSION

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pablo Whaley whose telephone number is (571)272-4425. The examiner can normally be reached on 9:30am - 6pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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